OLMESARTAN MEDOXOMIL

ALZOR®

20mg Film-Coated Tablet
40mg Film-Coated Tablet
ANGIOTENSIN II RECEPTOR BLOCKER

FORMULATION
Each film-coated tablet contains:
Olmesartan medoxomil, USP 20mg
Olmesartan medoxomil, USP 40mg

DESCRIPTION
20mg - White to off white coloured, circular, biconvex, film coated tablets plain on the both sides.
40mg - White to off white coloured, capsule shaped, biconvex, film coated tablets plain on the both sides.

INDICATION
Treatment of essential hypertension.

CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients. Second and third trimesters of pregnancy. Biliary obstruction. The concomitant use of Olmesartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m^2).

DOSAGE AND ADMINSTRATION
Adults
The recommended starting dose of Olmesartan medoxomil is 10 mg once daily. In patients whose blood pressure is not adequately controlled at this dose, the dose of Olmesartan medoxomil may be increase to 20 mg once daily as the optimal dose. If additional blood pressure reduction is required, Olmesartan medoxomil dose may be increased to a maximum of 40 mg daily or hydrochlorothiazide therapy may be added.
The antihypertensive effect of Olmesartan medoxomil is substantially present within 2 weeks of initiating therapy and is maximal by about 8 weeks after initiating therapy. This should be borne in mind when considering changing the dose of regimen for any patient.
Elderly (65 years or over)
No adjustment of dosage is generally required in elderly people. If up-titration to the maximum dose of 40 mg daily is required, blood pressure should be closely monitored.
Renal impairment
The maximum dose in patients with mild to moderate renal impairment (creatinine clearance of 20-60 mL/min) is 20 mg Olmesartan medoxomil once daily, owing to limited experience of higher dosages in this patient group. The use of Olmesartan medoxomil in patients with severe renal impairment (creatinine clearance < 20 mL/min) is not recommended, since there is only limited experience in this patient group.
Hepatic impairment
No adjustment of dosage recommendations is required for patients with mild hepatic impairment. In patients with moderate hepatic impairment, an initial dose of 10 mg Olmesartan medoxomil once daily is recommended and the maximum dose should not exceed 20 mg once daily. Close monitoring of blood pressure and renal function is advised in hepatically-impaired patients who are already receiving diuretics and/or other antihypertensive agents. There is no experience of Olmesartan medoxomil in patients with severe hepatic impairment, therefore use is not recommended in this patient group. Olmesartan medoxomil should not be used in patients with biliary obstruction.
Paediatric population
The safety and efficacy of Olmesartan medoxomil in children and adolescents below 18 years has not been established. Therefore, no recommendation on a posology can be made Olmesartan medoxomil should not be used in children below 1 year of age because of safety concerns and lack of data in this age group.
Method of administration
In order to assist compliance, it is recommended that Alzor tablets be taken at about the same time each day, with or without food, for example at breakfast time. The tablet should be swallowed with a sufficient amount of fluid (e.g. one glass of water). The tablet should not be chewed. Or as prescribed by the physician.

PHARMACODYNAMICS
Mechanism of action
Olmesartan medoxomil is a potent, orally active, selective angiotensin II receptor (type AT1) antagonist. It is expected to block all actions of angiotensin II mediated by the AT1 receptor, regardless of the source or route of synthesis of angiotensin II. The selective antagonism of the angiotensin II (AT1) receptors results in increase in plasma renin levels and angiotensin I and II concentrations, and some decrease in plasma aldosterone concentrations.
Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a significant role in the pathophysiology of hypertension via the type 1 (AT1) receptor.
Clinical efficacy and safety
In hypertension, Olmesartan medoxomil causes a dose-dependent, long-lasting reduction in arterial blood pressure. There has been no evidence of first-dose hypotension, of tachyphylaxis during long-term treatment, or of rebound hypertension after cessation of therapy.
Once daily dosing with Olmesartan medoxomil provides an effective and smooth reduction in blood pressure over 24 hour dose interval. Once daily dosing produced similar decreases in blood pressure as twice daily dosing at the same total daily dose.
With continuous treatment, maximum reductions in blood pressure are achieved by 8 weeks after the initiation of therapy, although a substantial proportion of the blood pressure lowering effect is already observed after 2 weeks of treatment. When used together with hydrochlorothiazide, the reduction in blood pressure is additive and coadministration is well tolerated.
The effect of Olmesartan on mortality and morbidity is not yet known.

PHARMACOKINETICS
Absorption and distribution
Olmesartan medoxomil is a prodrug. It is rapidly converted to the pharmacologically active metabolite, Olmesartan, by esterases in the gut mucosa and in portal blood during absorption from the gastrointestinal tract.
No intact Olmesartan medoxomil or intact side chain medoxomil moiety have been detected in plasma or excreta. The mean absolute bioavailability of Olmesartan from a tablet formulation was 25.6%.
The mean peak plasma concentration (Cmax) of Olmesartan is reached within about 2 hours after oral dosing with Olmesartan medoxomil, and Olmesartan plasma concentrations increase approximately linearly with increasing single oral doses up to about 80 mg.
Food had minimal effect on the bioavailability of Olmesartan and therefore Olmesartan medoxomil may be administered with or without food.
No clinically relevant gender-related differences in the pharmacokinetics of Olmesartan have been observed.
Olmesartan is highly bound to plasma protein (99,7%), but the potential for clinically significant protein binding displacement interactions between Olmesartan and other highly bound coadministered drugs is low (as confirmed by the lack of a clinically significant interaction between Olmesartan medoxomil and warfarin). The binding of Olmesartan to blood cells is negligible. The mean volume of distribution after intravenous dosing is low (16-29 L).
Biotransformation and elimination
Total plasma clearance was typically 1.3 L/h (CV, 19%) and was relatively slow compared to hepatic blood flow (ca 90 L/h). Following a single oral dose of ^{14}C-labelled Olmesartan medoxomil, 10-16% of the administered radioactivity was excreted in the urine (the vast majority within 24 hours of dose administration) and the remainder of the recovered radioactivity was excreted in the faeces. Based on the systemic availability of 25,6%, it can be calculated that absorbed Olmesartan is cleared by both renal excretion (ca 40%) and hepatobiliary excretion (ca 60%). All recovered radioactivity was identified as Olmesartan. No other significant metabolite was detected. Enterohepatic recycling of Olmesartan is minimal.Since a large proportion of Olmesartan is excreted via the biliary route, use in patients with biliary obstruction is contraindicated.
The terminal elimination half-life of Olmesartan varied between 10 and 15 hours after multiple oral dosing. Steady state was reached after the first few doses and no further accumulation was evident after 14 days of repeated dosing. Renal clearance was approximately 0.5-0.7 L/h and was independent of dose.
Pharmacokinetics in special populations
Older people (age 65 years and older)
In hypertensive patients, the AUC at steady state was increased by ca 35% in older people (65-75 years old) and by ca 44% in very old people (≥75 years old) compared with the younger age group. This may be at least in part related to a mean decrease in renal function in this group of patients.
Renal impairment
In renally impaired patients, the AUC at steady state increased by 62%, 82% and 179% in patients with mild, moderate and severe renal impairment, respectively, compared to healthy controls.
Hepatic impairment
After single oral administration, Olmesartan AUC values were 6% and 65% higher in mildly and moderately hepatically impaired patients, respectively, than in their corresponding matched healthy controls. The unbound fraction of Olmesartan at 2 hours post-dose in healthy subjects in patients with mild hepatic impairment and in patients with moderate hepatic impairment was 0.26% and 0.34% and 0.41%, respectively. Following repeated dosing in patients with moderate hepatic impairment, Olmesartan mean AUC was again about 65% higher than in matched healthy controls. Olmesartan mean Cmax values were similar in hepatically-impaired and healthy subjects. Olmesartan medoxomil has not been evaluated in patients with severe hepatic impairment.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Intravascular volume depletion
Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of Olmesartan medoxomil.
Other conditions with stimulation of the renin-angiotensin-aldosterone system
In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with other drugs that affect this system has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure. The possibility of similar effects cannot be excluded with angiotensin II receptor antagonists.
Renovascular hypertension
There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system.
Renal impairment and kidney transplantation
When Olmesartan medoxomil is used in patients with impaired renal function, periodic monitoring of serum potassium and creatinine levels is recommended. Use of Olmesartan medoxomil is not recommended in patients with severe renal impairment (creatinine clearance < 20 mL/min). There is no experience of the administration of Olmesartan medoxomil in patients with a recent kidney transplant or in patients with end-stage renal impairment (i.e. creatinine clearance <12 mL/min).
Hepatic impairment
There is no experience in patients with severe hepatic impairment and therefore use of Olmesartan medoxomil in this patient group is not recommended.
Hyperkalaemia
The use of medicinal products that affect the renin-angiotensin-aldosterone system may cause hyperkalaemia.
The risk, that may be fatal, is increased in elderly people, in patients with renal insufficiency and in diabetic patients, in patients concomitantly treated with other medicinal products that may increase potassium levels, and/or in patients with intercurrent events.
Before considering the concomitant use of medicinal products that affect the renin-angiotensin-aldosterone system, the benefit risk ratio should be evaluated and other alternatives considered (see also below section "Dual blockade of the renin-angiotensin-aldosterone system (RAAS)").
The main risk factors for hyperkalaemia to be considered are:
- Diabetes, renal impairment, age (> 70 years)
- Combination with one or more other medicinal products that affect the renin-angiotensin-aldosterone system and/or potassium supplements. Some medicinal products or therapeutic class of medicinal products may provoke a hyperkalaemia: salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptors antagonists, non-steroidal anti-inflammatory drugs (including selective COX-2 inhibitors), heparin, immunosuppressor as ciclosporin or tacrolimus, trimethoprim.
- Intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, worsening of renal function, sudden worsening of the renal condition (e.g. infectious diseases), cellular lysis (e.g. acute limb ischemia, rhabdomyolysis, extended trauma).
Close-monitoring of serum potassium in at risk patients is recommended.
Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE- inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended.
If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.
ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.
Lithium
As with other angiotensin- II receptor antagonists, the combination of lithium and Olmesartan medoxomil is not recommended.
Aortic or mitral valve stenosis; obstructive hypertrophic cardiomyopathy
As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.
Primary aldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin system. Therefore, the use of Olmesartan medoxomil is not recommended in such patients.
Sprue-like enteropathy
In very rare cases severe, chronic diarrhoea with substantial weight loss has been reported in patients taking Olmesartan few months to years after drug initiation, possibly caused by a localized delayed hypersensitivity reaction. Intestinal biopsies of patients often demonstrated villous atrophy. If a patient develops these symptoms during treatment with Olmesartan, and in the absence of other apparent etiologies, Olmesartan treatment should be immediately discontinued and should not be restarted. If diarrhoea does not improve during the week after the discontinuation, further specialist (e.g. a gastro-enterologist) advice should be considered.
Ethnic differences
As with all other angiotensin II antagonists, the blood pressure lowering effect of Olmesartan medoxomil is somewhat less in black patients than in non-black patients, possibly because of a higher prevalence of low-renin status in the black hypertensive population.
Pregnancy
Angiotensin II antagonists should not be initiated during pregnancy. Unless continued angiotensin II antagonists therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.
Other
As with any antihypertensive agent, excessive blood pressure decrease in patients with ischaemic heart disease or ischaemic cerebrovascular disease could result in a myocardial infarction or stroke.
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

DRUG INTERACTIONS
Interactions studies have only been performed in adults.
Effects of other medicinal products on Olmesartan medoxomil
Other antihypertensive medications
The blood pressure lowering effect of Olmesartan medoxomil can be increased by concomitant use of other antihypertensive medications.
ACE-inhibitors, angiotensin II receptor blockers or aliskiren
Clinical trial data shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as

hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.

Potassium supplements and potassium sparing diuretics

Based on experience with the used of other drugs that affect the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other drugs that may increase serum potassium levels (e.g. heparin) may lead to increases in serum potassium. Such concomitant use is therefore not recommended.

Non-steroidal anti- inflammatory drugs (NSAIDs)

NSAIDs (including acetylsalicylic acid at doses > 3g/day and also COX-2 inhibitors) and angiotensin-II receptor antagonists may act synergistically by decreasing glomerular filtration.

The risk of the concomitant use of NSAIDs and angiotensin II antagonists is the occurrence of acute renal failure. Monitoring of renal function at the beginning of treatment should be recommended as well as regular hydration of the patient.

Additionally, concomitant treatment can reduce the antihypertensive effect of angiotensin II receptor antagonists, leading to their partial loss of efficacy.

Bile acid sequestering agent colesevelam

Concurrent administration of the bile acid sequestering agent colosevelam hydrochloride reduces the systemic exposure and peak plasma concentration of Olmesartan and reduces t1/2.

Administration of Olmesartar medoxomil at least 4 hours prior to colesevelam hydrochloride decreased the drug interaction effect. Administering Olmesartan medoxomil at least 4 hours before the colesevelam hydrochloride dose should be considered.

Other compounds

After treatment with antacid (aluminium magnesium hydroxide), a modest reduction in bioavailability of Olmesartan was observed.

Effects of Olmesartan medoxomil on other medicinal products

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors and angiotensin II antagonists. Therefore use of Olmesartan medoxomil and lithium in combination is not recommended. If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Other compounds

Compounds which have been investigated in specific clinical studies in healthy volunteers include warfarin, digoxin, an antacid (magnesium aluminum hydroxide), hydrochlorothiazide and pravastin. No clinically relevant interactions were observed and in particular Olmesartan medoxomil had no significant effect on the pharmacokinetics or pharmacodynamics of warfarin or the pharmacokinetics of digoxin.

Olmesartan had no clinically relevant inhibitory effects on in vitro human cytochrome P450 enzymes 1A1/2, 2A6, 2C8/9, 2C19, 2D6, 2E1 and 3A4, and had no or minimal including effects on rat cytochrome P450 activities. Therefore in vivo interaction studies with known cytochrome P450 enzyme inhibitors and inducers were not conducted, and no clinically relevant interactions between Olmesartan and drugs metabolised by the above cytochrome P450 enzymes are expected.

ADVERSE REACTIONS

The most commonly reported adverse reactions during treatment with Olmesartan medoxomil are headache (7.7%), influenza-like symptoms (4.0%) and dizziness (3.7%).

Adverse reactions from Olmesartan medoxomil in clinical trials, post-authorisation safety studies and spontaneous reporting are summarized in the below table.

The following terminologies have been used in order to classify the occurrence of adverse reactions very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

MedDRA System Organ Class	Adverse reactions	Frequency
Blood and lymphatic system disorders	Thrombocytopenia	Uncommon
Immune system disorders	Anaphylactic reaction	Uncommon
Metabolism and nutrition disorders	Hypertriglyceridaemia	Common
	Hyperuricaemia	Common
	Hyperkalaemia	Rare
Nervous system disorders	Dizziness	Common
	Headache	Common
Ear and labyrinth disorders	Vertigo	Uncommon
Cardiac disorders	Angina pectoris	Uncommon
Vascular disorders	Hypotension	Rare
Respiratory, thoracic and mediastinal disorders	Bronchitis	Common
	Pharyngitis	Common
	Cough	Common
	Rhinitis	Common
Gastrointestinal disorders	Gastroenteritis	Common
	Diarrhoea	Common
	Abdominal pain	Common
	Nausea	Common
	Dyspepsia	Common
	Vomiting	Uncommon
	Sprue-like enteropathy	Very rare
Skin and subcutaneous tissue disorders	Exanthema	Uncommon
	Allergic dermatitis	Uncommon
	Urticaria	Uncommon
	Rash	Uncommon
	Pruritus	Uncommon
	Angioedema	Rare
Musculoskeletal and connective tissue disorders	Arthritis	Common
	Back pain	Common
	Skeletal pain	Common
	Myalgia	Uncommon
	Muscles spasm	Rare
Renal and urinary disorders	Haematuria	Common
	Urinary tract infection	Common
	Acute renal failure	Rare
	Renal insufficiency	Rare
General disorders and administration site conditions	Pain	Common
	Chest pain	Common
	Peripheral oedema	Common
	Influenza-like symptoms	Common
	Fatigue	Common
	Face oedema	Uncommon
	Asthenia	Uncommon
	Malaise	Uncommon
	Lethargy	Rare
Investigations	Hepatic enzymes increase	Common
	Blood urea increased	Common
	Blood creatine phosphokinase increased	Common
	Blood creatinine increase	Rare

USE IN PREGNANCY AND LACTATION

Pregnancy

The use of angiotensin II antagonists is not recommended during the first trimester of pregnancy. The use of angiotensin II antagonists is contra-indicated during the 2nd and 3rd trimester of pregnancy.

There is no controlled epidemiologiocal data on the risk with angiotensin II antagonists, similar risks may exist for this class of drugs. Unless continued angiotensin receptor blocker therapy is considered essential, patients planning pregnancy should be changed alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II antagonists should be stopped immediately, and if appropriate, alternative therapy should be started.

Should exposure to angiotensin II antagonists have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken angiotensin II antagonists should be closely observed for hypotension.

Breast-feeding

There is no information is available regarding the use of Olmesartan during breast-feeding, Olmesartan is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

Olmesartan has minor or moderate influence on the ability to drive and use machines.

Dizziness or fatigue may occasionally occur in patients taking antihypertensive therapy, which may impair the ability to react.

OVERDOSE AND TREATMENT

Only limited information is available regarding overdosage in humans. The most likely effect of overdosage is hypotension. In the event of overdosage, the patient should be carefully monitored and treatment should be symptomatic and supportive.

No information is available regarding the dialysability of Olmesartan.

PRECLINICAL SAFETY DATA

In chronic toxicity studies in rats and dogs, Olmesartan medoxomil showed similar effects to other AT1 receptor antagonists and ACE inihibitors; raised blood urea (BUN) and creatinine (through functional changes to the kidneys caused by blocking AT1 receptors); reduction in heart weight; a reduction of red cell parameters (erythrocytes, haemoglobin, haematocrit); histological indications of renal damage (regenerative lesions of the renal epithelium, thickening of the basal membrane, dilatation of the tubules). These adverse effects caused by the pharmacological action of Olmesartan medoxomil have also occurred in preclinical trials on other AT1 receptor antagonists and ACE inihibitors and can be reduced by simultaneous oral administration of sodium chloride.

In both species, increased plasma renin activity and hypertrophy/hyperplasia of the juxtaglomerular cells of the kidney were observed. These changes, which are a typical effect of the class of ACE inhibitors and other AT1 receptor antagonists, would appear to have no clinical relevance.

Like other AT1 receptor antagonists Olmesartan medoxomil was found to increase the incidence of chromosome breaks in cell cultures in vitro. No relevant effects were observed in several in vivo studies during Olmesartan Medoxomil at very high oral doses of up to 2000mg/kg. The overall data of a comprehensive genotoxicity testing suggest that Olmesartan is very unlikely to exert genotoxic effects under conditions of clinical use.

Olmesartan medoxomil was not carcinogenic, neither in rats in a 2 year study nor in mice when tested in two 6 month carcinogenicity studies using transgenic models.

In reproductive studies in rats, Olmesartan medoxomil did not affect fertility and there was no evidence of a teratogenic effect. In common with other angiotensin II antagonists, survival of offspring was reduced following exposure to Olmesartan medoxomil and pelvic dilatation of the kidney was seen after exposure of the dams in late pregnancy and lactation. In common with other antihypertensive agents, Olmesartan medoxomil was shown to be more toxic to pregnant rabbits than to pregnant rats, however, there was no indication of fetotoxic effect.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without a prescription.

FOR SUSPECTED ADVERSE DRUG REACTION, REPORT TO FDA: www.fda.gov.ph
Seek medical attention immediately at the first sign of any adverse drug reaction.

STORE AT TEMPERATURES NOT EXCEEDING 30°C.

ALZOR® is a registered trademark of Ajanta Pharma Philippines, Inc.

REGISTRATION NUMBER
Alzor® 20mg: DR-XY47888
Alzor® 40mg: DR-XY47904

AVAILABILITY
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